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(54) Title: NEW FORMULATION FOR INHALATION HAVING A POURED BULK DENSITY OF 0.28 TO 0.38 G/ML, A PROCESS FOR PREPARING THE FORMULATION AND THE USE THEREOF

(57) Abstract

A dry powder composition comprising one or more potent pharmaceutically active substances and a carrier substance, all of which are in finely divided form, wherein the formulation has a poured bulk density of from 0.28 to 0.38 g/ml is useful in the treatment of respiratory disorders.

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NEW FORMULATION FOR INHALATION HAVING A POURED BULK DENSITY OF 0.28 TO 0.38 G/ML, A PROCESS FOR PREPARING THE FORMULATION AND THE USE THEREOF

Field of the Invention

The present invention provides a new pharmaceutical formulation, its preparation and its use.

Background to the Invention

Potent drugs for administration by inhalation are generally formulated in association with carriers such as lactose because of the problem of preparing accurate doses. When such drugs are diluted, variations in the weight of the formulation result in a smaller drug dosage variation rate compared with when they are not diluted. These formulations have generally consisted of coarse particles of the carrier with fine particles of the drug, which combination is generally known as an ordered mixture.

The invention provides an improved formulation which, in systems designed to imitate inhalation has been found to give an improved dispersion of the drug.

Description of the Invention

According to the invention there is provided a dry powder composition comprising one or more potent pharmaceutically active substances and a carrier substance, all of which are in finely divided form, wherein the formulation has a poured bulk density of from 0.28 to 0.38 g/ml, preferably from 0.30 to 0.36 g/ml.

The poured bulk density according to the present invention is measured using known techniques, for example those described in "Powder testing guide: Methods of measuring the physical properties of Bulk powders" L. Svarovsky, Elsevier Applied Science 1987, pp 84-86.

A potent pharmaceutically active substance suitable for use in the invention is, for example, an antiarrhythmic drug, tranquiliser, cardiac glycoside, hormone, hypertensive drug, antidiabetic or anticancer drug, sedative or analgesic drug, antibiotic, antirheumatic drug, immunotherapy, antifungal or antihypotension drug, vaccine, antiviral drug, protein (e.g. insulin), peptide, vitamin, or a cell surface receptor blocker. It is preferably a glucocorticosteroid, particularly one which is metabolised rapidly, for example beclomethasone dipropionate (BDP), beclomethasone monopropionate (BMP), flunisolide, triamcinolone acetonide, fluticasone propionate, ciclesonide, budesonide, rofleponide or derivatives thereof, momethasone, tipredane, RPR 106541 and/or a β2-agonist such as terbutaline, salbutamol, formoterol, salmeterol, TA 2005, pircumarol or a pharmaceutically acceptable salt thereof; and/or a prophylactic agent such as sodium chromoglycate or nedocromil sodium.

Suitable physiologically acceptable salts include acid addition salts derived from inorganic and organic acids, for example the chloride, bromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate, ascorbate, acetate, succinate, lactate, glutarate, gluconate, tricarballylate, hydroxynaphthalene-carboxylate or oleate salts or solvates thereof.

The carrier substance is preferably a mono-, di- or polysaccharide, a sugar alcohol or another polyol. Suitable carriers are, for example, lactose, glucose, raffinose, melezitose, lactitol, maltitol, trehalose, sucrose, mannitol; and starch. Lactose is particularly preferred, especially in the form of its monohydrate.

The ingredients of the formulation according to the invention must both be in a finely divided form, i.e. their mass median diameter should generally be less than 10 μm, preferably from 1 to 7 μm, as measured by a laser diffraction instrument or a coulter counter. The ingredients may be produced in the desired particle size using methods known to those of skill in the art, e.g. milling, micronisation or direct precipitation.

The combination of budesonide and formoterol is particularly preferred. Formoterol is preferably used in the form of its fumarate, especially the dihydrate.

When the one or more potent pharmaceutically active substances used in the invention are formoterol and budesonide, the molar ratio of formoterol to budesonide in the composition of the invention is preferably from 1:2500 to 12:1, more preferably from 1:555 to 2:1, most preferably from 1:133 to 1:6. The composition according to the invention is preferably formulated to provide a daily dose of formoterol of from 2 to 120 nmol (more preferably from 7 to 70 nmol). When formoterol is used in the form of formoterol fumarate dihydrate, the composition is preferably formulated to provide a daily dose of formoterol fumarate dihydrate of from 1 to 50 μg, more preferably from 3 to 30 μg. The composition according to the invention is preferably formulated to provide a daily dose of budesonide of from 45 to 2200 μg, more preferably from 65 to 1700 μg.

More preferably the composition of the invention comprises, as a unit dose, 6μg of formoterol fumarate dihydrate and 100μg of budesonide, or 4.5μg of formoterol fumarate dihydrate and 80μg of budesonide, either of which can be administered up to four times a day. Alternatively the composition of the invention comprises, as a unit dose, 12μg of formoterol fumarate dihydrate and 200μg of budesonide, or 9μg of formoterol fumarate dihydrate and 160μg of budesonide, either of which is administered once or twice a day.

Most preferably the composition used in the invention comprises, as a unit dose, 6μg of formoterol fumarate dihydrate and 200μg of budesonide, or 4.5μg of formoterol fumarate dihydrate and 160μg of budesonide, either of which is administered up to four times a day. Alternatively the composition of the invention comprises, as a unit dose, 12μg of formoterol fumarate dihydrate and 400μg of budesonide, or 9μg of formoterol fumarate dihydrate and 320μg of budesonide, either of which is administered once or twice a day.

According to the invention there is further provided a process for preparing a composition according to the invention which comprises

(a) micronising the one or more potent pharmaceutically active substances and the carrier substance;

(b) optionally conditioning the product; and

(c) spheronizing until the desired bulk density is obtained.

The process preferably further comprises a low energy remicronisation step after step (b).

The formulation according to the invention may be made by conventional techniques known *per se*. Such production processes generally comprise micronising the ingredients to the required size, removing any amorphous areas on the particles obtained by, for example, the methods described in WO 92/18110 or WO 95/05805 and then agglomerating, spheronising and sieving the powder obtained. The size of the agglomerates obtained is preferably in the range of from 100 to 2000 μm, more preferably from 100 to 800 μm. The bulk density of the formulation produced may be adjusted by varying the components and the process empirically, for example the bulk density can be increased by lengthening the time in which the particles are tumbled in a spheronising device.

In solid-solid mixing, one of the most important features is to ensure content uniformity. The major problem encountered in the powder mixing of fine powders is the inability of mixers to break down powder agglomerates. It has been found that a remicronisation step after the conditioning step of the fine powder with low energy input is advantageous. It should generally be carried out using enough energy to break down powder agglomerates but not with so much energy that the size of the particles themselves is affected. Such a step gives a composition wherein the active substance and carrier substance are substantially uniformly distributed, having for example a relative standard deviation of less than 3% (preferably less than 1%) and does not disturb the crystallinity of the fine particles.

The formulation according to the invention may be administered using any known dry powder inhaler, for example the inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler, for example Turbuhaler (trade mark). The invention further provides use of a composition according to the invention in the manufacture of a medicament for use in therapy. The composition according to the invention is useful in the treatment of respiratory disorders, particularly asthma. The invention also provides a method of treating a patient suffering from a respiratory disorder which comprises administering to the patient a therapeutically effective amount of a composition according to the invention.

The invention is illustrated, but not limited, by reference to the following Examples.

Example 1

0.0315 Parts of formoterol fumarate dihydrate and 2.969 parts of lactose monohydrate are mixed in a tumbling mixer (Turbula) to an evenly distributed mixture, whereafter the mixture is micronised in a spiral jet mill using a pressure and feeding rate suitable to obtain a particle size of less than 3 μm (mass median diameter as measured by a coulter counter). The micronised particles were then treated using the method disclosed in WO 95/05805 to remove amorphous regions in their crystal structure. The powder was then agglomerated by feeding the powder into a twin screw feeder (K-Tron), sieving in an oscillating sieve (0.5 mm mesh size), spheronising in a rotating pan with a peripheral speed of 0.5m/s for 4 minutes and then sieving again using the same sieve, then spheronising once more for 6 minutes before final sieving (mesh size 1.0 mm) giving a powder with a bulk density of 0.32g/ml.

Example 2

Example 1 was repeated but the powder was remicronised in a spiral jet mill at a lower pressure (about 1 bar) after micronisation and conditioning such that the step of treating the

particles in the manner described in WO 95/05805 was not required giving a powder with a bulk density of 0.32 g/ml.

Example 3

9 Parts of budesonide and 91 parts of lactose monohydrate were micronised separately in a spiral jet mill at a pressure of about 6-7 bars to give a particle size of less than 3 μm before being mixed thoroughly in a Turbula mixer. Before mixing, the lactose monohydrate powder was conditioned according to the method described in WO 95/05805. The mixture was remicronised in a spiral jet mill at a pressure of only about 1 bar to obtain a uniform mixture. The powder was then agglomerated and spheronised as described in Example 1 to obtain a bulk density of 0.35 g/ml.

Example 4

60 Parts of terbutaline sulphate were micronized to a mass medium diameter of less than 2 μm in a Alpin mill 100AFG and thereafter conditioned according to the method described in US 5562923. 40 Parts of lactose monohydrate were micronized (Alpin mill 100AFG) down to a mass medium diameter of less than 3 μm and thereafter conditioned according to the method described in WO 95/05805. The micronized and conditioned terbutaline sulphate and lactose monohydrate were mixed thoroughly in a Turbula mixer. The mixture was remicronised in a spiral jet mill at a pressure of only about 1 bar to obtain an evenly distributed mixture. The powder was then agglomerated and spheronised as described in Example 1 to obtain a bulk density of 0.28 g/ml.

Example 5

Example 4 was repeated with 30 parts of terbutaline sulphate and 70 parts of lactose monohydrate to give a powder with a bulk density of 0.31 g/ml.

Example 6

5.2 Parts of formoterol fumarate dihydrate and 896.8 parts of lactose monohydrate were mixed in a tumbling mixer to an evenly distributed mixture, whereafter the mixture was micronised in a spiral mill using a pressure and feeding rate suitable to obtain a particle size of less than 3 μm (mass medium diameter as measured by a coulter counter). The micronised particles were then treated using the method described in WO 95/05805 to remove amorphous regions in their crystal structure. 98 parts of micronised budesonide were added and the mixture was remicronized at a lower pressure in a spiral jet mill to a homogenous mixture. The powder was then agglomerated by feeding into a screw feeder (K-Tron), sieved in an ocillating sieve (0.5 mm mesh size), spheronised in a rotating pan with a speed of 23 rpm for 10 minutes, then sieved again (0.5 mm mesh size), spheronised once more before final sieved (0.8 mm mesh size) to give a powder with a bulk density of 0.34 g/ml.

Example 7

Example 6 was repeated with identical conditions but using 5.2 parts of micronized formoterol fumarate dihydrate, 798.8 parts of micronized lactose monohydrate and 196 parts of micronized budesonide. The bulk density obtained was 0.34 g/ml.

Claims

1. A dry powder composition comprising one or more potent pharmaceutically active substances and a carrier substance, all of which are in finely divided form, wherein the formulation has a poured bulk density of from 0.28 to 0.38 g/ml.

2. A composition according to claim 1 wherein the one or more potent pharmaceutically active substances are budesonide and formoterol.

3. A composition according to claim 1 or 2 wherein the bulk density is from 0.30 to 0.36 g/ml.

4. A composition according to claim 1, 2 or 3 wherein the active substance and carrier substance are substantially uniformly distributed.

5. A composition according to any one of claims 1 to 4 for use in the treatment of a respiratory disorder.

6. A process for preparing a composition according to claim 1 which comprises

(a) micronising the one or more potent pharmaceutically active substances and the carrier substance;

(b) optionally conditioning the product; and

(c) spheronizing until the desired bulk density is obtained.

7. A process according to claim 6 which comprises a low energy remicronisation step after step (b).

8. Use of a composition according to any one of claims 1 to 4 in the manufacture of a medicament for use in therapy.

9. A method of treating a patient suffering from a respiratory disorder which comprises administering to the patient a therapeutically effective amount of a composition according to any one of claims 1 to 4.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/00040

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/72, A61K 31/165, A61K 31/58
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, USPATFULL, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5551489 A (EVA A. C. TROFAST ET AL), 3 Sept 1996 (03.09.96), column 2, line 8 - line 15 --	1-9
X	US 4590206 A (RAYMOND B. FORRESTER ET AL), 20 May 1986 (20.05.86), column 4, line 15 - line 21; column 4, line 46 - line 47 --	1-9

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 May 1998	19 -05- 1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte...ational application No.
PCT/SE 98/00040

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 9
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Claim 9 is directed to method of treatment of the human or animal body by therapy methods practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claims. The search has been based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

29/04/98

International application No.
PCT/SE 98/00040

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5551489 A	03/09/96	AU 7826194 A	01/05/95
		CZ 9600942 A	12/06/96
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